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EXAMINER

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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ADVISORY ACTION

The amendment filed on 7/13/09, under 37 CFR 1.116, in reply to the final rejection has been entered and considered but is not deemed to place the application in condition for allowance for the reasons below. Applicants' arguments are addressed below.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 28, 31-33, 35, 37, 39, 40 and 42-47 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained.

Applicants argue:

Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) which when administered to a subject result in aspects of the immune response being altered, along with changes in cytokine levels that are useful in the treatment of diseases such as cancer and infectious diseases. This class of oligonucleotides is described throughout the specification and the ability of these oligonucleotides to produce an immune response is not only described but data is presented in vitro and in vivo using a number of different CpG containing oligonucleotides. The data presented in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3 and Example 4), and production of IL-6 (Example 8) as well as other cytokines (IFN-gamma and IL-12. Accordingly, one aspect of the invention involves the use of synthetic oligonucleotides

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containing CpG motifs to induce a pattern of immune response, which at the time of filing the application was recognized as being capable of causing reductions in tumors and infections.

Applicants' arguments are carefully considered but are not persuasive. While at the time of the effective filing date of the instant application (1994), bacterial DNA comprising CpG motifs was indeed known to be immunostimulatory, mere immune response does not predict the efficacy of the instant oligonucleotide containing an unmethylated wherein the oligonucleotide comprises 5'-TGACGTT-3' wherein the oligonucleotide comprises a phosphorothioate modification in treating any type of cancers, viral infections/diseases or bacterial infections/diseases.

The nature/scope of the instant invention is drawn to the boosting of a subject's immune response to treat or eliminate any type of cancer, any type of viral infection or any type of bacterial infection. The scope of 'subject' set forth includes humans, dog, cat, horse, cow, sheep, goat, chicken, monkey, rat, mouse etc. See specification p. 11 last two lines. The teachings of the specification are limited to *in vitro* and *in vivo* data that demonstrate that unmethylated cytosine –guanine containing oligonucleotides stimulates B-cells and induces the production of cytokines and data that demonstrates induction of IL-6 in mice injected with said oligonucleotides. The specification at the time of filing does not correlate the immune responses generated by administering an oligonucleotide containing an unmethylated wherein the oligonucleotide comprises 5'-TGACGTT-3' wherein the oligonucleotide comprises a phosphorothioate modification *in vitro* with treating the breadth of cancers, viral infections or bacterial infections. Treatment of cancer, viral infections or bacterial infections is very complex and dependent on many factors.

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Applicants argue:

A review article by Trinchieri et al. (Blood, V.84, December 15, 1994, p. 4008) describes IL-12 in the production of cytotoxic lymphocytes. The role of IL-12 in antitumor immunity is discussed at length on pages 4021-4022 of the article. Studies conducted using transplantable tumors in experimental animals and showing a drastic effect of IL-12 in decreasing tumor growth and metastasis formation have been described. The Office alleges that the portion of Trinchieri et al. cited is drawn to the work of Brunda et al. (Journal Leukocyte Biology, V.55, February 1994) which teaches that "future clinical trials with this cytokine will determine if the activity demonstrated in animals can be translated into efficacy against human malignancies." The Examiner acknowledges and Applicant agrees that Brunda et al. teaches that IL-12 has potent antitumor and anti-metastatic activities in several murine tumor models (Office Action page 9). The fact that Brunda et al. mentions that future studies need to be conducted in humans is irrelevant to the finding of IL-12 as a cytokine that has potent antitumor and antimetastatic activity in several murine tumor models. According to the MPEP, there should be no burden on the Applicant to present *in vivo* evidence in order to overcome the enablement rejection. "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." MPEP Section 2107.03.

Applicants' arguments are carefully considered but are not persuasive. The portion of Trinchieri cited is drawn to the work of Brunda et al (J. Exp. Med vol. 178, Oct 1993, p. 1223-1230). The Brunda et al study teaches that IL-12 has potent antitumor and anti-metastatic activities in several murine tumor models through an immune mediated T-cell dependent mechanism (p. 1228 column 2 last paragraph). However, Brunda et al teaches that future clinical trials with this cytokine will determine if the activity demonstrated in animals can be translated into efficacy against human malignancies (p. 1228 column 2 last paragraph). In addition, the instant claims are not limited to treatment in murine animals but include humans as well as other animals. See instant specification bottom of p. 11 and claim 37. Brunda et al teaches the differences in responses to IL-12 stimulation of human versus murine NK or T cells (see above) and teaches that more work needs to be done to determine if the activity demonstrated in animals can be translated into efficacy against human malignancies (p. 1228 column 2 last paragraph). The Office is not requiring evidence from clinical trials to establish

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enablement but is merely stating the teachings of the prior art at the time the instant invention was made regarding the unpredictability of predicting the efficacy of IL-12 in treating cancer in humans from animal studies. Neither Brunda et al or Trinchieri et al discloses treatment with CpG oligonucleotides.

The review by Trinchieri et al also discloses the use of IL-12 in treatment of viral infections (see p. 4020 column 2 under virus infections). Trinchieri et al teaches that IL-12 is a potentiator of delayed type hypersensitivity and of cytotoxic lymphocyte responses and should be expected to play a role in the resistance against virus infections but however little information is available on either the importance of endogenous IL-12 or the effect of IL-12 treatment in viral infections. Trinchieri teaches that surprisingly IL-12 inhibited rather than enhanced CTL generation in Lymphocytechoriomeningitis virus infected mice and the inhibitory effect was evident at particularly high doses of IL-12. While the instant oligonucleotide may stimulate production of IL-12 in a subject having a viral infection it is not clear how much IL-12 is produced and whether the amount produced inhibits the CTL response to viral infection. The specification does not correlate the amount IL-12 production in response to the instant oligonucleotide with inhibition or enhancing CTL activity and thus one of skill in the art cannot predict based on the guidance in the specification and in the art how the IL-12 produced correlates with treatment of any type of viral infection (or any type of cancer or bacterial infection for that matter) especially in view of the fact that IL-12 in high doses inhibits the antiviral response to LCMV infection. Although, Trinchieri et al also teaches that studies in murine models suggest IL-12 may play a role in combating *Listeria monocytogenes* (an intracellular bacteria) infection (see p. 4018 column 2 under *Listeria monocytogenes*), the

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instant specification does not correlate the strength of the immune response generated by the instant oligonucleotide with treatment of *Listeria* or any other type of bacteria and studies in murine models with IL-12 may not predict efficacy in humans due to the differences in the responses to IL-12.

Applicants argue:

The Office has dismissed the teachings of Morris et al. (Infection and Immunity, 1982, 35(2):533-536), Baumgarth et al. (Journal of Virology, 1994, 68(11):7575-7581), Woodworth and Simpson (Am. J Path., vol 142 (5): 1544-55 (1993), Schneider (Genitourin. Meal., 1993, vol 69 (3): 165-73), and Morris et al (Br J Obstet Gynecol, 1983, vol 90(5):412-20) stating that these references do not disclose the induction of an immune response to CpG oligonucleotides. These references were not cited by Applicant to demonstrate the ability of CpG oligonucleotides to induce an immune response, but rather to show that induction of specific cytokines was useful in the treatment of cancers and infections. Thus, one skilled in the art would recognize that a drug useful for boosting such cytokines would be useful in the treatment of viral infection. Morris et al. showed that IFN γ is produced from two human T-lymphoblastoid lines upon virus infection (see page 536, left column). Baumgarth et al. disclose that IFN γ has been identified as a key factor in immune responses to viral infections and demonstrated IFN γ production in response to influenza virus. Woodworth and Simpson employed HPV-infected and non-infected cells and analyzed their lymphokine secretion profiles. The authors report that while normal cervical cells constitutively secreted IL-1 alpha, IL-1 beta, IL-1 RA, IL-6, IL-8, TNF-alpha, and GM-CSF, the HPV-infected cell lines "exhibited significant down-regulation of IL-1 beta, IL-6, TNF-alpha, IL-8, and GM-CSF" (page 1548, right column, 1st paragraph, Figure 3, and Table 1). The authors note in their discussion that "if the constitutive release of lymphokines is involved in maintaining normal immunocompetence in the cervical mucosa, then decreased secretion might provide a more favorable environment for persistence of HPV-infected cells" (page 1552, right column, 2nd paragraph). In the abstract of Schneider, it is stated that the impaired cellular immune response upon genital HPV infection is characterized by depletion of T helper/inducer cells and/or Langerhans cells and impaired function of natural killer cells and/or the infected keratinocytes. Morris et al. studied wart virus infections with no evidence of cervical intraepithelial neoplasia and noted "a patchy reduction or total absence of Langerhans' cells in the epithelium" (page 415, left column, 2^d paragraph). Langerhans' cells are antigen-presenting cells derived from monocytes. There was also a "striking reduction in the number of T lymphocytes". Thus, one of ordinary skill in the art

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would recognize the therapeutic value of CpG in treating a viral infection such as papilloma virus infection.

Applicants' arguments have been carefully considered but are not persuasive. The Office disagrees with Applicants assertion that the Office dismissed the teachings cited by Applicants. Each and every one of the teachings was carefully considered in light of the scope of the invention being claimed but was not found to be persuasive. As stated even though Applicants submit that IFN-gamma is produced from human T-lymphoblastoid line upon virus infection (Morris et al Infection and Immunity, 1982 35(2):533-536, p. 536 left column); and IFN-gamma has been identified as a key factor in immune responses to viral infections and that there is IFN-gamma production in response to influenza virus (Baumgarth et al. Journal of Virology, 1994, 68 (11):7575-7581); and that lymphokines, NK cells, Langerhans Cells are important in maintaining normal immunocompetence in the cervical mucosa and thus may play a role in treatment of viral infections including papillomavirus virus (Woodworth and Simpson. Am. J. Path., vol 142(5):1544-55, 1993; Schneider. Genitourin. Med., 1993, vol 69 (3): 165-73; Morris et al. Br J Obstet Gynecol, 1983, vol 90(5):412-20); all these references do not disclose the induction of an immune response to CpG oligonucleotides and as evidenced by Trinchieri et al cytokine production does not predict efficacy for treatment of a viral infection and may be dependent on how much of the cytokine is produced. Treatment or elimination of HIV in HIV infected patients with the instant oligonucleotide is made more complex because of the impaired ability of HIV infected patients to produce IL-12 (Trinchieri et al p. 4020 to 4021 under IL-12 and HIV) which Applicants submit is important in treating viral infections. If a subject having HIV infection has an impaired IL-12 (important for stimulating NK cells which produce IFN

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gamma) producing ability then it is unpredictable based on Applicants disclosure and the teaching of the art that the instant oligonucleotide can treat or eliminate said HIV infection.

Applicants argue:

The teachings with respect to Sfondiri et al. and Krieg et al. have been dismissed and it is alleged that these are limited to only one type of cancer in a murine subject and that it is difficult at best to use observations with CpG ODNs in routine studies to predict accurately the effects of TLR9 activation in humans. The post-filing references were not presented to demonstrate that every CpG oligonucleotide has been used in humans to treat cancer and infectious disease as a stand alone. Rather the references were presented as evidence that, as Applicant's specification set forth, CpG oligonucleotides in fact were demonstrated following the invention to be useful in treating cancers and infectious disease in a subject. The fact that one reference is limited only to a specific cancer and is in a mouse and the other is limited to one oligonucleotide in humans, doesn't diminish the evidentiary purpose of the references. The Office further notes that the role of IL-6 in the early response to bacterial infection has been demonstrated by Liu et al. (Infection and Immunity, Oct. 1992, p. 4402-4406). According to the Office, the time of administration of the oligonucleotide is critical for the innate response to have an effect and has not been addressed by the specification. The Office also asserts that contrary to Applicant's arguments, the mere presence of the CpG dinucleotide does not predict the efficacy in treatment of any type of cancer or bacterial or viral infections and that according to Kataoka et al. (Jpn. J. Cancer Res vol. 83 p.244-247, 1992), the active oligonucleotides contained hexameric palindromic sequence structures that are essential for biological activity. The invention is directed to a class of molecules that are useful in the treatment of diseases such as cancer and infectious diseases. Applicant was the first to recognize that synthetic oligonucleotides containing unmethylated CpG irrespective of their sequence or length could replicate these immune activating effects of bacterial DNA. Some of these immunostimulatory oligonucleotides comprise a palindrome. Importantly, oligonucleotides such as ODN 1, 1d, 3df and 3Md do not contain a palindrome and yet are immunostimulatory. The data provided in the specification is evidence that immunostimulatory activity results from the CpG motif, regardless of whether or not the motif is present in a palindrome.

The fact that the art suggests that some oligonucleotides may work better than others is not sufficient to contradict the teaching that in general CpG oligonucleotides are immunostimulatory under the appropriate conditions.

One of skill in the art would have recognized that the pattern of immune response elicited by these oligonucleotides would be useful in the treatment of cancer and infectious disease. Data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. Furthermore, a number of clinical trials involving administration of bacterial DNA to humans showed positive effects in various cancer patients (Tokunaga et al Jpn. J.

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Infect. Dis 52, 1-I 1, 1999), thereby confirming the utility of the CpG oligonucleotides in the treatment of cancer.

Applicants' arguments are carefully considered but are not persuasive. Again, the Office disagrees with Applicants assertion that the Office dismissed the teachings cited by Applicants. Each and every one of the teachings was carefully considered in light of the scope of the invention being claimed but was not found to be persuasive.

Applicants argument that post-filing references Sfonidiri et al and Krieg et al are evidence that, as Applicant's specification set forth, CpG oligonucleotides in fact were demonstrated following the invention to be useful in treating cancers and infectious disease in a subject, does not take away the fact that these references also teach the unpredictability of using results in mice to predict efficacy in humans. Krieg et al (Proc Am Thorac Soc vol. 4 p. 289-294, 2007, see p. 289 left column under *the role of TLR9 in the mechanism of action of CpG ODNs*) teaches that it is difficult at best to use observations with CpG ODNs in murine studies to predict accurately the effects of TLR9 (i.e. the cellular receptor for CpG ODN) activation in humans because the cellular patterns of TLR expression vary between species so the results of TLR stimulation (in mice, for example) may not be predictive of what will occur in another (humans). Even after filing reference disclosing the use of a CpG oligonucleotide comprising the instant 5'-TGACGTT-3' (submitted in reply to the Office action dated 1/8/08 –see Applicants arguments of 7/18/08) demonstrates all the complexity involved in treating one type of cancer in a mice model. Sfondrini et al was considered and analyzed in detail in the previous Office action mailed 8/26/08, see p. 8-10. As set forth previously, Sfondrini et al (FASEB 2002 vol. 16 p. 1749-1754) provided by Applicants teaches an oligonucleotide ODN 1668 that includes TGACGTT. Sfondrini et al does teach that phosphorothioate modified ODN 1668 prevented the

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development of spontaneous mammary tumors in 4 out of 11 mice after 380 days (FVB-NeuN transgenic mice were treated i.p. with CpG ODN every 10 days starting at 10 wk of age) while all untreated mice developed mammary tumors before 305 days of age (p. 1750 under oligonucleotides and under results and p. 1751 fig. 1). However, the results of Sfondrini are limited to treatment of one type of (cancer mammary adenocarcinoma tumors) in a murine subject while the instant claims are partially drawn to treating any type of cancer in a subject including humans who has cancer. Applicants submit that at the time the priority patent application was filed it was known in the art that induction of interferon gamma, IL-12, IL-6 as well as NK cell activation was useful in the treatment of cancer. However, Brunda et al (J. Exp. Med vol. 178, Oct 1993, p. 1223-1230) teaches the differences in responses to IL-12 stimulation of human versus murine NK or T cells in vitro in that said human cells secrete tumor necrosis factor while said murine T cells do not produce TNF (see p. 1228 column 1 last paragraph). Thus, there are differences in the response to IL-12 between human and murine NK or T cells and Brunda et al (J. Exp. Med vol. 178, Oct 1993, p. 1223-1230) teaches that more work needs to be done to determine if the activity demonstrated in animals can be translated into efficacy against human malignancies (p. 1228 column 2 last paragraph). In addition, conditions for treating the mice already having the mammary adenocarcinoma tumors varied (see Sfondrini et al). In mice bearing small spontaneous mammary tumors, no significant tumor inhibition was observed using increased i.p. doses and increased frequency of administration whereas significant inhibition was observed when 40 ug of the CpG ODN were injected at the tumor site for 5 days (p. 1751 column 2 first complete paragraph). Sfondrini et al further demonstrates the complexity of treating the tumors in mice. Mice inoculated i.v. with N202.1A carcinoma cells

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formed significantly fewer lung metastases after 4 wk if treated with CpG ODNs (20 ug/mouse) 4h before or 2h after tumor cell inoculation compared with control and mice administered 40 ug CpG ODN administered i.p. 4 hours before and in the 4 subsequent days had inhibition of experimental metastases although still incomplete. No inhibitory effect was observed when CpG-ODN was administered 48 h after N202.1A cell injection. Thus, even in mice, the treatment of one type of cancer i.e. mammary adenocarcinoma with phosphorothioate CpG ODN comprising TGACGTT is complex and is dose, route and schedule of treatment dependent.

Applicants' assertion that the fact that one reference is limited only to a specific cancer and is in a mouse and the other is limited to one oligonucleotide in humans and doesn't diminish the evidentiary purpose of the references, is carefully considered but the references have to be considered in light of the full scope of what is being claimed. The specification defines immune system deficiency as follows:

A disease or disorder in which the subject's immune system is not functioning in normal capacity *or* in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small' cell), ovary breast, prostate, colon as well as carcinomas and sarcomas) or viral (e.g. HIV, herpes), fungal (e.g. Candida sp.), bacterial or parasitic (e.g. Leishmania, Toxoplasma) infection in a subject.

See p. 11 lines 21 to 26 of the specification.

Applicants in their arguments of 2/23/09 specify that they are claiming the latter type of immune system deficiency and that the claims do not encompass the treatment of a disorder in which the immune system is not functioning in a normal capacity such as the disorders listed on pages 3-4 of the Office action mailed 8/26/08 and that the claims have been amended to clarify this. Thus, the nature/scope of the instant invention is drawn to the boosting of a subject's

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immune response to treat or eliminate any type of cancer, any type of viral infection or any type of bacterial infection. The scope of 'subject' set forth includes humans, dog, cat, horse, cow, sheep, goat, chicken, monkey, rat, mouse etc. See specification p. 11 last two lines.

As to Liu et al, efficacy of recombinant IL-6 in treating one type of intracellular bacterial infection in mice was time dependent and was not effective when administered 24hr post infection but effective at 4hr post infection. This demonstrates the role of IL-6 in the early response to bacterial infection (Liu et al. Infection and Immunity, Oct. 1992, p.4402-4406). Therefore, the time of administration of said oligonucleotide is critical for the innate response to have an effect. Also said oligonucleotide may be more efficacious when administered before bacterial or viral infection as demonstrated by Liu et al before the bacteria have the chance to evade the immune system. Liu et al also does not disclose CpG oligonucleotides for treating bacterial infection and the specification does not correlate any immune response generated by the instant oligonucleotide with treating intracellular or extracellular bacterial infection.

Further as to treatment of cancers in a subject who has a cancer, Kataoka et al (Jpn. J. Cancer Res vol. 83 p.244-247, 1992, cited in IDS) show anti-tumor activity of synthetic oligonucleotides containing cytosine-guanine in a murine tumor system with sequences from cDNA encoding proteins of *Mycobacterium bovis* BCG. Said anti-tumor activity correlated with NK cell activity and interferon inducing activities. However, Kataoka et al does not disclose an oligonucleotide containing an unmethylated wherein the oligonucleotide comprises 5'-TGACGTT-3' wherein the oligonucleotide comprises a phosphorothioate modification. Furthermore, Kataoka et al teaches that the efficacy of the BCG bacterial DNA derived

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oligonucleotides used was not only dependent on the presence of the CG motif but the sequence context of the CG motif was important i.e. mere presence of the CG motif does not predict efficacy. The active oligonucleotides contained a hexameric palindromic sequence that contained the CG motif (see Kataoka et al p. 245) and Kataoka et al concluded that particular hexameric structures are essential for expressing the biological activities of oligonucleotides and for antitumor activity.

Applicants' assertion that they were the first to recognize that synthetic oligonucleotides containing unmethylated CpG irrespective of their sequence or length could replicate these immune activating effects of bacterial DNA. Some of these immunostimulatory oligonucleotides comprise a palindrome and that oligonucleotides such as ODN 1, 1d, 3df and 3Md do not contain a palindrome and yet are immunostimulatory is carefully considered but is not persuasive. The fact that that synthetic oligonucleotides containing unmethylated CpG irrespective of their sequence or length are immunostimulatory does not predict the efficacy in treating or eliminating a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small' cell), ovary breast, prostate, colon as well as carcinomas and sarcomas) or viral (e.g. HIV, herpes) or bacterial infection in a subject. Furthermore, the position of the CpG motif and the sequence flanking the CpG motif *does* play a critical role in determining the immunostimulatory activity of the CpG motif containing oligonucleotide. See Krieg et al. (Nature 1995:374, 6522: 546-549, cited in IDS).

Applicants assertion that the fact that the art suggests that some oligonucleotides may work better than others is not sufficient to contradict the teaching that in general CpG oligonucleotides are immunostimulatory under the appropriate conditions is not persuasive. The

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claims are not drawn to whether or not the instant CpG is immunostimulatory but the nature/scope of the instant invention is drawn to the boosting of a subject's immune response to treat or eliminate any type of cancer, any type of viral infection or any type of bacterial infection.

One of skill in the art at the time of filing (1994) could not predict the efficacy of one type of phosphorothioate modified unmethylated cytosine guanine containing oligonucleotide comprising 5'-tgacgtt- 3' for the treatment of all types of cancer in subjects having cancer. Hiyashi et al (Proc. Japan Acad., 70, Series B (1994) 205-209) demonstrates that different types of cancers at different stages of progression respond differently to treatment. Applicants submit that Hayashi et al teaches the importance of interferon(IFN)-gamma in treatment of cancer. However, in Hiyashi et al (Proc. Japan Acad., 70, Series B (1994) 205-209) while the BCG cell wall skeleton treatment induced detectable levels of IFN-gamma in all surviving patients as compared to those who did not survive their cancer, the reference is drawn to treatment of cancer patients with BCG-Cell Wall Skeleton not to the treatment with CpG oligonucleotides. Furthermore, not all cancer patients produced IFN-gamma in response to the BCG cell wall and the different responses may be due to the stage of cancer, type of cancer and initial treatment (surgical operation and/or radiation or chemotherapy, see table 1 p. 207). Thus, the efficacy of the BCG cell wall in treating these patients was dependent on many factors and not merely production of IFN gamma – not all the patients were able to produce IFN-gamma in response to BCG cell wall. Also, it is impossible to predict from Hiyashi et al who used BCG cell wall, whether subjects with different cancers and/or at different stages of other types of treatment

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and/or at different stages of cancer would respond to the instant oligonucleotide to produce the cytokines that can treat said cancer.

Applicants cite U. S. Patent No. 4,883,662 (Nov. 28, 1989) to Stout for the teaching that increasing NK cells in the blood of cancer patients should be an advantage in cancer treatment (summary of the invention) because NK cells have known activity against tumor cells (abstract). The patent in Example II teaches the administration of a parvovirus immunized positive serum to a terminally ill cancer patient and there is no teaching of administration of CpG oligonucleotides. Furthermore, the patients condition deteriorated during therapy and at the end of the therapy had noted no unusual qualitative differences during the treatment period. Furthermore the patient finally died even though the serum increased the NK cell population in that patient. The Stout patent demonstrates that mere increase of NK cells in a cancer patient does not predict that said cancer is treated.

Applicants' argument that a number of clinical trials involving administration of bacterial DNA to humans showed positive effects in various cancer patients (Tokunaga et al Jpn. J. Infect. Dis 52, 1-11, 1999), thereby confirming the utility of the CpG oligonucleotides in the treatment of cancer is carefully considered but is not persuasive. Applicants' submission that one skilled in the art would recognize the utility of treating cancer and infection based on the disclosure and data provided in the instant patent application is carefully considered but is not persuasive. The fact that an applicant has disclosed a specific utility for an invention and provided a credible basis supporting that specific utility does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph (MPEP 2107.01. General Principles Governing Utility Rejections).

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As mentioned previously the data provided in the specification is directed to *in vitro* and *in vivo* data that demonstrate that unmethylated cytosine –guanine containing oligonucleotide induce an immunostimulatory response including stimulation of B-cells and induction of the production of cytokines and *in vivo* data that demonstrates *in vivo* induction of IL-6 in mice injected with said oligonucleotides. The specification is devoid of any data correlating the immune responses generated by the instant oligonucleotide with treatment or elimination of any type of cancer or any type of bacterial or viral infection in any subject.

The rejection is maintained.

Status of Claims

Claims 28, 31-33, 35, 37, 39, 40 and 42-47 are rejected. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645

/David J Blanchard/
Primary Examiner, Art Unit 1643